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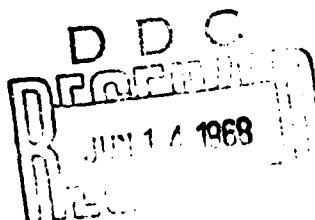
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LIVE-VACCINES AGAINST DISEASES OF ANIMALS

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MAY 1966

U. S. ARMY

FORT DETRICK, FREDERICK, MARYLAND

## LIVE-VACCINES AGAINST VIRUS DISEASES OF ANIMALS

(Following is the translation of an article by Anton Mayor, published in the German language periodical Zent. Back, 191; 1963, pages 37-50. Translation performed by Constance L. Lust.)

A transition is taking place in our fields and on our farms which cannot be judged yet in its sociological and economic effects. New tasks are placed before the veterinarian who is responsible for the welfare of the animal herds, in the extensive change which is occurring in agriculture. Today, under the effect of industrialization of agriculture, demands are made on house-animals which are more specialized and often more unnatural than in earlier times. Through better hygienic treatment and conditions, better feeding, etc. they are no longer fully exposed. The consequences are disturbances in health, which results in a higher susceptibility to infectious diseases, which often appear in stock as well as in work animals.

The crowding of large herds in relatively small areas in farms and feeding or milking stations has created a danger of epidemics whose seriousness is not yet fully recognised. This danger is most serious on pig-and fowl farms, where several thousand animals are often crowded into a very small space. But even beef raising is beginning to be subject to a similar process of "industrialisation". In an animal population which lives under such crowded conditions, an epidemic can spread unchecked and the germ that caused it can, under certain conditions, become ever more virulent in the swift passage from animal to animal. Moreover, in the course of this quick spreading, the germ often undergoes a series of selective changes and mutations which often lead to a "specialization" of the germ in characteristics which were not dominant before the beginning of the epidemic. This differentiation of viruses in the course of epidemics has long been a recognised fact. But since the discovery of tissue cultures, in which we can artificially produce hundreds of virus-passages in a relatively short time and study the individual selective and mutation processes experimentally and under controlled conditions, we know more about this important epidemiological process and recognise the danger of epidemics in massive herds.

In addition there is the large volume of trade and travel, which promotes the spread of viruses to a degree never before experienced. Daily our herds are infected with new germs with which the animals have had no previous contact, and against which they therefore have no natural protection. Even the animal epidemics which were formerly localised for the most part in the tropics have approached our borders through international travel - and especially by airplanes. Epidemics like african hog- and horse plague, rinderpest, african and asiatic hoof and mouth disease, blue-tongue in sheep, lung infections of beef and pox infections of sheep, only to mention a few, threaten to become a permanent danger to our herds.

Veterinarians, veterinarian institutions and Science are following this development carefully. We are forced more and more to abandon the traditional individualistic animal-medicine in favor of collective medicine, that is the preventive care of herds and entire animal populations. The "keeping healthy" is now more important than the "curing."

The best specific preventive method for the protection of our herds against infectious diseases has proved to be prophylactic inoculation. These inoculations are especially important in the case of virus-generated epidemics, because we have up to now not been able to combat virus diseases with either chemicals or antibiotics, as is possible in the case of bacterial diseases.

Large medical circles still hold to the belief that it is very simple to combat animal epidemics. The ill and infected animals, as well as those suspected of being infected are slaughtered, suitable isolation techniques are used, and the epidemic is controlled. This may once have been partially true, but today this is not enough, although we are by no means ready to abandon our old and tested methods of combating epidemics with slaughter, isolation and infection. Under certain epidemiological conditions these are still the best methods of control, not to mention the fact that we have not yet been able to inoculate effectively against all dangerous epidemics, even though science is working feverishly at the development of newer, better means of inoculation. There are many other points that must be taken into account, e.g. the character of the epidemic, its effect on people, and the structure of the farms.

The search for the most effective methods of combating animal epidemics is, therefore, contingent upon many factors and it must be determined anew for each occasion, which methods are to be used. In the combating of chronological infections of a creeping nature, like beef tuberculosis for example, the relentless slaughter of all infected animals has proved to be most useful. And in the treatment of herds infected with brucellosis, it is still necessary to resort to slaughter. On the other hand, it must be clearly stated that the old methods of the veterinary authorities have failed in the treatment of many other epidemics, especially those that spread rapidly and are highly contagious in the present agricultural structure and under conditions of constant contamination from outside.

Under these conditions, prophylactic protective inoculations are the means with which animal husbandry can be freed of the constant difficulties which sweep over it again and again with each new epidemic. The center of interest is the live-virus vaccines which combat virus diseases of animals.

The basis of the development of live-virus vaccines against animal diseases are the same as those in human medicine. The names of Jenner, Pasteur, v. Behring and Ehrlich stand at the beginning. All current live-virus vaccines in human- and animal medicine contain a- virulent or weak virulent, but still reproducing virus strains, which no longer produce a cyclical general illness with infection of the typical organs after suitable application of the person or animal. But since they retain their

specific immunizing and antigenic properties, the inoculated being is protected against falling ill for a certain period of time.

The production of vaccines is carried out by means of test animals, chicken embryos, or tissue cultures in the usual way.

In order to obtain useful virus strains one uses the traditional methods of selection and mutation in various hostsystems. As starting material for the virus one should, if possible, use original field material with a broad antigen spectrum, the following procedures have proved themselves in practice or are being tested further:

1. Constant passages on small test animals or in chicken- pigeon or duckembryos,
2. Constant passages in homologous or heterologous cell cultures in which the medium, pH-value or temperature can be changed if desired,
3. Clone-Selection process with the help of the Plaque-or End-dilution technique,
4. Isolation and passing on of virus-material from harvests that have been stored for some time at a lower temperature in various hosts, especially in cell cultures,
5. Exchanges between homologous and heterologous hosts, perhaps using embryonic cell systems,
6. Subcultivation of latently infected cell cultures or of single cells from infected cell cultures which were not destroyed by the virus replication, followed by the raising of the virus in primary cultures,
7. Separation of genetically heterogeneous natural virus populations in an electrical field (biological evaluation of the constants of motion of the different virus particles) and selective breeding of the useable particles.

The oldest and at the same time the most successful procedure for obtaining suitable virus strains is still the search for related natural virus types with the same immunization spectrum. The classical example of this is the Vaccine virus which has common antigenic and immunizing components with Variola virus, and which has been used successfully to vaccinate against human pocks since the time of E. Jenner. The parallel to this in animal medicine is the Pigeon pock virus. It has immunizing characteristics similar to Fowl pock virus and has been used for a long time to inoculate fowl against fowl pocks. In the meantime the similarity between the Variola-, Cow pocks-, Vaccine-, and Mouse pocks virus and between lumpy-skin virus of beef and the sheep pocks virus and between the fibrom- and myxomavirus of rabbits.

In recent years a new development has begun in the field of related properties between various virus types. It began with the discovery of the relationship between the measle- and Stompe virus. Later the similarity of the Rinderpest virus was discovered. Today it is considered certain, that there are closely related and immunologically similar properties between these three virus-types, which are, however, of a

different nature from those between the above-mentioned pox viruses. Very recently further relationships between various different virus types have been uncovered: between the Adeno virus (type 4) of the human and the hepatitis virus of the dog and a similar relation between the diarrhea virus of cattle and the hog-plague virus (1-6). These relationships have not yet made it possible to vaccinate against the Staupvirus of dogs with a measles virus or against the hog plague with a diarrhea virus in the sense of a complex immunity as in the case of protective inoculation against pox, but they do encourage further research, perhaps in the direction of para-specific vaccination. In the search for new-vaccine strains this development must be followed closely. Similar relationships must certainly exist between many other virus types, which could perhaps be useful for inoculation. For example; Rhino tracheitis of cattle and Herpes infection were until recently considered to be individual completely unconnected virus diseases. Today we know that both diseases are caused by the same virus type and that there are no serological and immunological differences between the causes of these two diseases. There may perhaps exist similar relationships between human and animal virus diseases.

In any case, human and animal medicine should work much more closely together in this field than has been the case previously, and devote more time and money to comparative virology.

A vaccination campaign with live-virus vaccines leads to a decrease in the infection-rate and morbidity. The live vaccines immunize better than vaccines from inactive viruses and they provide protection that is more certain and lasts longer. It is especially important that inoculation with live vaccines leads to a complex immunity, that is, to humoral and cellular immunization processes, like those that would result from the natural course of an infection. This complex protection is especially important in diseases that affect the mucous membranes, since the humoral protection provided by inoculation with inactive viruses, is not adequate to combat these diseases alone. A further advantage of live vaccines is the short time lapse between vaccination and the beginning of immunity. Live vaccines can therefore still be used successfully in situations where an epidemic has already begun in a herd.

But all live vaccines have disadvantages as well as advantages.

The situation is very similar to human medicine. Many live vaccines produce a certain amount of danger for the patient and for his surroundings, since it is not always possible to find the proper combination for maximum effectiveness against the disease as well as a minimum of harmful side-effects for the patient. If the attenuation process is carried too far the immunizing qualities are quickly lost. A certain amount of replication of the vaccine virus is necessary in the patient to assure a sufficient number of immunizing processes. The live vaccines therefore have a much stronger effect on the patient's system than do those made from inactive viruses. The course of the vaccination is dependent not only on the virus strain used, but also on the susceptibility of the patient to the reaction as well as his resistance. While it is possible to analyse the biological

characteristics of the virus strain exactly, which makes it a known factor, the reaction of the individual patient is unknown.

With most vaccine materials the strain is released in some manner into the surrounding area. Non-immunized subjects may be endangered by this procedure. Likewise the danger to humans must be recognized. For example it would be impossible to vaccinate against viruses of dog or rinderpest with measles virus. The vaccination of horse- and rinderpox with variola virus would be dangerous. However, very little attention is given to the processes. While humans are protected with pox vaccines, however, every now and then a number of pox outbreaks occur in animals especially in beef, horse and pigs. Other live vaccines of humans must also be scrutinized more carefully in this connection.

In animal medicine the behavior of the vaccine virus in the vaccinated subject is of importance. If a viremia exists for longer periods after inoculation, then the virus could be deposited (and replicate) in the inner organs such as lymph nodes or bone marrow. When these animals are then slaughtered the virus could be carried throughout the world especially in frozen meat products.

Also under discussion is whether rapid passage of the vaccine virus in the natural host can lead to a reversion of virulence. This is particularly important in massed animal colonies, where the virus can run through passages very rapidly. Also the so-called spontaneous mutations which may occur during replication of the vaccine virus are potentially dangerous. In the vaccinated animals the altered virus appears along with the known vaccine strain. The mutated strain is then, of course, extremely difficult to assay.

With live vaccines completely different conditions exists for the veterinary authorities than with inactivated vaccines. Often a general vaccination is in order and the neighboring states (lands) are of necessity involved.

With live vaccines of animals there is a greater danger of contamination with foreign "silent" viruses which are not easily detected than in human medicine. For vaccine production cell systems are used which could harbor latent infections of various viruses. For example when using chick embryos for vaccine production contamination with all those viruses that are carried in chickens is a very real possibility. Besides *Salmonella*, various pplo type and TB bacteria chick embryos may carry various chicken viruses. The most important are leukosis virus, Newcastle virus, chick bronchitis virus, Psittacosis-Ornithosis virus, chick encephalitis, Cello virus, and GAL virus which belongs to the Adenovirus group. If live vaccines are prepared against fowl virus disease utilizing chick embryos, then the transmission of a foreign virus is especially dangerous since the new hosts after vaccination are again chickens. In this connection fowl pox vaccine, vaccines against fowl pest and chick encephalitis vaccine are important.

Cell cultures, regardless of whether they are primary cultures or permanent strains, may contain latent virus infections. Those conditions became known generally in monkey kidney cultures during the production of the polio virus vaccine. This is very similar in other animal cell cultures.

The latent infections of host systems during vaccine production is also becoming more important in new developments in the area of viruses as a cause of tumors. We know today that, besides the widespread autonomous tumor inducing viruses, many other viruses (perhaps all) are capable of influencing the cell genome and induce tumors this way. This process is dependent on many other factors, such as genetic constitution as well as physiological reasons. Changing hosts appears to play an important role in this phenomenon. An infection with heterologous virus types may be dangerous, since it cannot replicate optimally in foreign host systems.

The considerations to use live vaccines in animal medicine are based in large part on economic factors. Basically a vaccine is only utilized when the cost of vaccination is considerably less than the damage resulting from infection. Since live vaccines can be produced cheaper, they are gaining more importance in animal medicine. For example, for the treatment of a chicken, which has a production value of (2 DM Deutsche Mark, 0.50 cents) only vaccines which cost much less can be employed.

The total loss during an epidemic or illness is calculable from the number of cases times the average loss per sick or dead animal. The total costs of vaccination are comprised of number of animals times the cost of vaccination. This simple comparison cannot be made for every case. Often the total loss in an animal population resulting from an infection is difficult to determine. Various stages of infections are possible in an epidemic, sometimes the classical type is seen, other times subclinical infection result, and still other times latent infections occur which are carried along in the hosts. A typical case is hog pest. In many cases of virus infections of the respiratory, digestive and reproductive organs the virus merely prepares the way for bacterial or mycotic infections which are much more dangerous than the original virus illness. Economic factors do not always represent the best, or only, way of looking at the problem. The immunization of our dogs against rabies or hepatitis is a case. The worth of valuable animals cannot only be measured in terms of money. Nevertheless, the economic considerations naturally are dominant.

The method of vaccination with live vaccines is also determined by economic factors in most cases in animal medicine.

The cheapest and simplest method of dispensing the vaccine is via the drinking water. An example is the vaccine put into drinking water for atypic fowl pest. They are the so-called lentogenous strains (B<sub>1</sub>, La Sota, F-strain) neuropathologic index cannot exceed 0.2 in day-old chicks. The virulence of this strain is rather weak. In Germany only the production of the vaccines of strain B<sub>1</sub>, as per Hitchner 1948, is permitted. This produces no illness after intracerebral inoculation in day old chicks. The vaccine is isolated from embryos or from tissue culture.

Since the Hitchner R<sub>1</sub>-virus multiplies readily in pig-kidney cultures, without losing its immunizing properties, a vaccine can be made which is free of other fowl viruses (7, 8, 9, 10). The Hitchner drinking-water-vaccine has found general usefulness. Chicks of between 3-4 days old can be vaccinated safely this way. But, since the immunity does not last in these young animals, vaccination is done several times. Generally these animals are vaccinated first at 1-4 weeks of age, the second time at 8-12 weeks and again just prior to maturity (ability to lay eggs). While laying they can be vaccinated every 4 months. Broilers in the U.S.A. are only vaccinated once, when 10 days old. This immunity lasts until time of slaughter. After vaccination these animals are under veterinary observation because of the release of the vaccine virus.

Other drink-water-vaccines of fowl are those against infectious bronchitis of chickens, and chick encephalomyelitis. Both vaccines are made in embryonated eggs, but are not entirely satisfactory and are consequently forbidden in Germany. But, because of the high incidence of chick encephalomyelitis the introduction of this vaccine is being considered despite the relatively high virulence of the vaccine strain.

A drinking-water-vaccine for hogs (analogous to polio vaccine) is the cultured vaccine against Teschen illness of hogs. The base is an attenuated Teschen virus (more than 100 passage in hog kidney cultures). It protects young hogs after intracerebral or intraspinal administration (11, 12). Since vaccination of pigs against polio is prohibited in Germany, we have no practical experience in this regard. Presently we treat this illness by (Kaulung?) (Koule = club) killings?

Similar to the "water" vaccines are aerosol vaccines. This method is also used mainly with fowl. All the vaccines mentioned earlier for the water route can also be aerosolized. Usually this route of vaccination is not used initially, but rather as a 2nd or booster vaccination.

Other special vaccination procedures especially with fowl are the eye drop method, anus or other mucous membranes. These methods are used while still relatively virulent. They are not allowed in Germany. An example is the vaccine for fowl laryngotracheitis. Here the vaccine is put on the throat mucous membrane. The virus is to cause a localized reaction there without infecting the respiratory organs. Immunity develops in 9 days and lasts for 1 year. After 7-9 days the vaccine virus cannot be found in feces or in the trachea. Animals are vaccinated at 2-4 months of age. The vaccine is made from eggs and contains 50% glycerine (13, 14). The mucous membrane is rubbed with a brush until slightly reddish. The vaccine strains should preferably contain a wide immunization spectrum. The vaccine has been used in the eye method also. The reaction is mild and immunity lasts 1 year.

Intranasal vaccination is also used with fowl. This method may also be used with larger animals. Boegel (16) developed a live vaccine for para-influenza -3- infections of beef which was administered intranasally. This virus is widespread in beef herds and causes many respiratory syndromes.

The virus was attenuated via 83 passages in calf kidney cultures. Vaccination of young calves is possible even if they are still protected passively via colostrums. Greater protection is afforded if after 1 year a 2nd vaccination is performed. Bovine lung infections can also be prevented by intranasal vaccination. Egg vaccines are common. Partial immunity lasts for one year. Protection lasts as long as after a natural infection (18).

Cutaneous vaccination should be mentioned. This is, of course, well recognised from pox-vaccination of humans. Similar methods are used with fowl in animal medicine. About 20 feathers are plucked on the upper leg and the vaccine is rubbed in. This is also called the feather-follicle method. The vaccine is derived from pigeon pox virus. The vaccination against Pustulardermatitis of sheep and goats is also a cutaneous vaccine. These live vaccines are made from tissue culture and vaccination is carried out via needles injected under the tail (17). Immunization protects for at least one year.

All other live vaccines against virus infections of animals are administered intramuscularly (perenterally) or subcutaneously. These are the vaccines against distemper and hepatitis of dogs, african horse pest, rinderpest, blue-tongue virus of sheep, sheep pox, hog pest, american horse encephalomyelitis, louping ill of sheep, infectious rhinotrachitis, virus-diarrhea of beef, myxomatosis of rabbits and hoof and mouth disease. Several of these are not completely satisfactory and are still under further development; hoof and mouth disease, horse encephalomyelitis, myxomatosis of rabbits. A complete chapter could be devoted to distemper vaccination alone.

In connection with hoof and mouth disease it should be mentioned: Despite the effective inactivated vaccine against hoof and mouth disease no good live vaccine has been developed, even though many labs throughout the world are working on this problem. In several countries attenuated strains are available. Their efficacy is being tested presently. The strains were attenuated via chick embryo, rabbits and via the mouse. Large-scale field trials have been performed in Africa, Near East and in South America. It was found that the vaccines were either too virulent (a high percentage of infection occurred) or the vaccine did not immunize well. In Germany we have tried to attenuate the strain via tissue culture. The results of trials showed (thus far) that the live vaccine was more effective with no side effects. However, in actual field trials our results were extremely disappointing. The attenuated strain behaved much differently here. Many vaccine-infections resulted. This is further complicated by the many strains (7 types). Presently we are using genetically defined strains. As soon as these results come in we will publish further data concerning this. We were most interested in vaccinating our hogs, which were difficult to treat with the inactivated strains. We can't treat hoof and mouth disease effectively until both hogs and beef can be immunized completely. It is our experience that hogs will only be protected optimally with live vaccines if the individual farmer is willing to accept a certain amount of illness because of vaccination. These illnesses usually do not bother the animals more than a few days. It is likely

that a totally innocuous (mild) vaccine will not be forthcoming. However, even before then much further work will be needed until a practical live vaccine for hoof and mouth disease is available.

Thus far the discussion has concerned itself with topics about live vaccines which are already in use in animal medicine. Not all of them are completely effective or without side effects. The number of vaccines in use is, however, so large that vaccine-calendars must be used for the individual animal types, as is sometimes done in human medicine. Of great value are combination-vaccines, which simultaneously can act against several illnesses.

Finally I would like to discuss the diseases of our animals for which we have no vaccines as yet. Generally these are virus diseases which leave only a minimal or no immunity. Two groups have to be differentiated.

Group 1; african hog pest, infectious anemia of horses and the large group of tumor causing viruses (leukosis etc). Not much about the pathogenesis of these diseases is known as yet, and vaccines are still far in the future. It is possible that for some of these infections no vaccines will ever be made. We use other methods to combat these diseases today in veterinary medicine.

Group 2; diseases of respiration, digestion, reproduction which affect many animals. The most important to us are beef and calf illnesses and grippes of pigs. It will be difficult to develop vaccines against this group of illnesses, but not impossible.

A definite characteristic of beef and calf illnesses is the great affinity of the pathogens for mucous membranes of the respiratory, digestive and reproductive system. The pattern of illness is for this reason seldom specific for any particular pathogen. The characteristics of the illness rather depend on numerous factors; virulence of the pathogen, secondary bacterial infection (or mycotic) which often determine the severity of illness. A resistance factor of the host and conditions in the surroundings also play an important role. Another major role is played by the colostrum which the young receive from mothers quickly after birth. Depending on the quality of the passive protection the infection may take other courses.

Clinically either the picture of feverous breathing-sickness or that of a feverous enteritis is seen, and mixed forms of both can occur. Epidemiologically the diseases appear especially in the fall in cattle populations. The different germs that are responsible for the diseases are widespread in our cattle herds. The herds develop active immunity with increasing age. Therefore the infections appear preferentially in young fully susceptible animals. The active immune cattle transferred their protection to the young via the colostrum. This passive immunity diminishes within a few weeks, afterward the young animal is fully susceptible again. Every cattle population has to ward off different germs and usually become immune only to those strains in their specific areas. When new calves are bought they are exposed to the germs and thus become infected. Every year our

herds have to contend with several types of infections. The germs, organism population of surroundings not only work together in causing illness in many different ways, they also depend on each other at the beginning and end of an altercation.

For a long time we were ignorant of these complex occurrences. Since we are now aware of them, we see possibilities for the development of vaccines which may be able to protect our animals prophylactically. A thorough study of the pathogenesis shows that most often the host-germ-reactions occur locally. Only later, and not always is virus transmitted to other cell systems and organs responsible for antibody formation via blood and the lymphatic system.

From an immunological point of view, these processes often have little effect on the overall host, so that the invading germ does not come into direct contact with the sites responsible for immunity. These infections can immunize certain sites rapidly such as membranes, without protecting the total host. Therefore a second infection may be elicited by the same germs.

If one takes into account the epidemiological, pathogenetic and immunogenic characteristics it may be possible by correctly using vaccines to immunize artificially against these virus illnesses which appear primarily locally. The artificial immunization may even be more effective than that resulting from the natural infection. The animals may be immunized locally cutaneously via mucous membranes and then simultaneously parenterally to protect them from infections that occur in a cyclic fashion. In practice we vaccinate intranasally and intramuscularly. This method of vaccination has a further advantage. We can vaccinate calves immediately after birth, because their passive immunity cannot diminish this artificial immunization. The maternal protection is purely humoral. With intranasal protection an effect is exerted on the mucous membranes of the periphery which are not well protected by the passive method. The vaccine-virus can accumulate in these areas and can initiate the immune responses.

With the respiratory and digestive illnesses of swine similarly complex mechanisms are probably involved. In all these illnesses infection agents can be isolated which until now have been characterized only partially. Next to virus types important pathogens here are pplo (SRP agens) organisms, germs which stand intermediate between viruses and bacteria.

Pplo organisms and Miyagawa organisms are widespread in animals and man. The Miyagawanellen are involved in bird and pig, as well as cattle illnesses. They have been implicated in cattle encephalomyelitis and for mastitis. Psittacosis and ornithosis germs are also in this group. Pplo infections play a major role in pigs and in respiratory illnesses of fowl. It is an important task for the science of immunology to develop vaccines to protect our animals prophylactically against these widespread, sometimes harmless, sometimes pathogenic, organisms. Perhaps live vaccines will also be developed here. This is for the future, but if our animals are to be protected adequately it will have to be done.

I have tried to discuss the most important problems in connection with live-vaccine protection against virus infections of our animal stands. Much is still unexplained, but we can be satisfied with the accomplishments thus far. Especially in the area of preventive vaccination great progress has been achieved in the last years. Many vaccines have been developed recently to go along with the many others already in use. Knowledge about the replication mechanism of the pathogen, its pathogenesis, have helped greatly in developing vaccines, however, much more work is needed in this direction. Not only are individuals and whole populations protected against sickness and death, but modern vaccines helped to lessen the great epidemiological, social-medical, political and economic problems which constantly threaten man with dangerous infectious diseases.

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